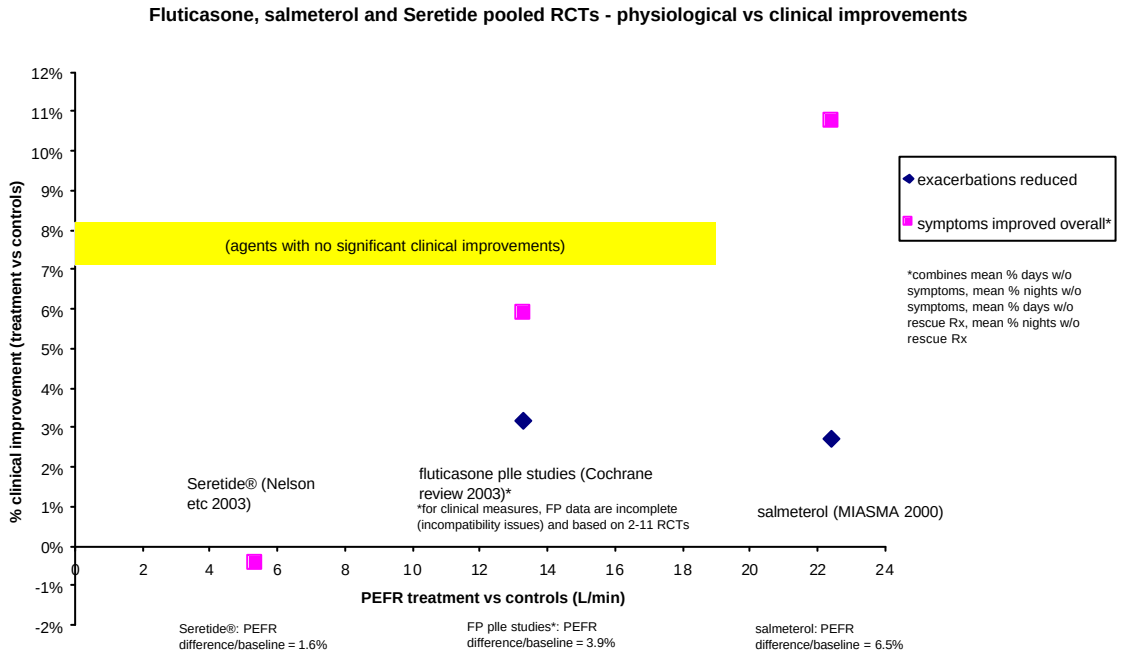
Effectiveness of combined ICS/LABAs delivery devices versus concurrent ICS and LABA via separate inhalers

In summary:

- There is little evidence that combination LABA/ICS products improve compliance over concurrent use of separate ICSA and LABA inhalers.
- There is newly emerging evidence that combination LABA/ICS products may be physiologically more effective than concurrent use of ICSs and LABAs.
- However, the extent of these improvements in physiological measures (which are but intermediate or surrogate outcomes) has been overstated. The true extent of peak expiratory flow rate (PEFR) reduction is 11% (using relative risk, not odds ratio).
- In addition, there were no differences in clinically relevant outcomes for combination LABA/ICS products.
- Separate analysis of withdrawals and adverse events (not performed in the industry-funded Seretide® meta-analysis) shows significantly higher rates of reported adverse events with Seretide®.
- Compared with salmeterol (and even fluticasone), Seretide® has much smaller changes in physiological effects, reflected in nil clinical improvements. Note that neither Seretide® nor fluticasone have been able to demonstrate clinically significant improvements in pooled analyses (figure 1).

Figure 1



- Hence, the advice from the British, GINA and New Zealand asthma guidelines still applies, that there is no difference in clinical efficacy between combination and concurrent (separate devices) LABA/ICS.

Compliance with combination LABA/ICS devices

The recently updated joint British Thoracic Society/Scottish Intercollegiate Guidelines Network asthma guidelines (BTS/SIGN guidelines) (section 11.2.2, page i59) state "Combination inhalers have not been shown to improve compliance in the medium to long term."[1]

The BTS/SIGN guidelines cite as evidence for the above statement a double-blind RCT comparing nedocromil/salbutamol combination with nedocromil alone[2], an open-label RCT of combination vs. concurrent terbutaline (short-acting beta2 agonist) and budesonide (ICS)[3], and 70% long-term compliance in a fluticasone RCT[4] (a somewhat curious citation, but perhaps because compliance was higher than in the other two studies).

In three out of four identified RCTs for Seretide® (Bateman etc 1998, Chapman etc 1999, Van den Berg etc 2000 below), mean compliance (actual use/expected) was respectively reported at 91%, 96% and 93% for combination LABA/ICS, versus 89%, 95% and 93% for concurrent LABA/ICS use via separate inhalers. These formally combine to give a non-significant 1% difference in (already high) compliance (Peto one-step relative risk (RR) 1.01, 95% confidence interval (CI) 0.99-1.03) (detailed in table 3 below). In the other RCT (Aubier etc 1999 below), compliance was stated to be high in all patients (regardless of regime).

These Seretide® RCT data were however complicated by Seretide® patients needing to use concurrent placebo inhaler, in order to maintain participant's blinding (double dummy design). Hence they do not allow for differences in convenience,[5] nor fully answer the question "Does the use of a single combination LABA/ICS inhaler improve compliance, beyond that gained using concurrent two separate inhalers?"

That said, compliance rates in the control groups in the Seretide® clinical trials were high. This suggests that the need to use two inhalers at the same time is not necessarily a key cause of poor compliance with asthma preventive inhalers.

The 2002 revised Global Strategy for Asthma Management and Prevention (GINA) guidelines state "Fixed combination inhalers are more convenient for patients, may increase compliance, ensure that the long-acting beta2-agonist is always accompanied by a glucocorticosteroid"[6] Note however that no evidence was given to support the claims of either greater convenience (although this does seem plausible) nor increased compliance.

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[1] British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003;58 Suppl 1:i1-94. http://www.sign.ac.uk/guidelines/published/support/guideline63/download.html

[2] Braunstein GL, Trinquet G, Harper AE. Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination. Compliance Working Group. Eur Respir J. 1996 May;9(5):893-8.

[3] Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? Eur Respir J. 1994 Mar;7(3):504-9.

[4] van Grunsven PM, van Schayck CP, van Deuveren M, van Herwaarden CL, Akkermans RP, van Weel C. Compliance during long-term treatment with fluticasone propionate in subjects with early signs of asthma or chronic obstructive pulmonary disease (COPD): results of the Detection, Intervention, and Monitoring Program of COPD and Asthma (DIMCA) Study. J Asthma. 2000 May;37(3):225-34.

[5] Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med. 1990 Sep;150(9):1881-4.

[6] National Heart, Lung, and Blood Institute , National Institutes Of Health. Global Strategy for Asthma Management and Prevention, revised 2002. (Scientific information and recommendations for asthma programs. NIH Publication No. 02- 3659). p108. http://www.ginasthma.com/workshop.pdf

International guidelines re efficacy of combination LABA/ICS devices

The recent New Zealand adult asthma guidelines[7] (page 40) state "Dry powder devices that combine both LABA and ICS in one unit are now available. Such combination dry powder devices have similar, but not improved, clinical effectiveness as giving the same medication via separate devices [1+]" (citing one RCT[8]). "Although combination dry powder devices may appear more convenient, the fixed dosing of such devices makes titration of the ICS portion of the dose more difficult."

The BTS/SIGN guidelines (section 4.4.3, page i22) cite grade 1++ evidence in an evidence table[9] detailing four identified RCTs for Seretide® (Bateman etc 1998[10], Chapman etc 1999[11], Van den Berg 2000[12], Aubier etc 1999[13]). On this basis the guidelines state "There is no difference in efficacy in giving inhaled steroid and long-acting beta2 agonist in combination or in separate inhalers".

Note however that there was no attempt with the BTS/SIGN guidelines to pool the results of the four Seretide® RCTs.

The 2002 revised GINA guidelines (p 108) state "Controlled studies have shown that delivering glucocorticosteroids and long-acting beta2- agonists together in a combination inhaler is as effective as giving each drug separately (Evidence B)."

Note the evidence cited for the GINA statement is misreferenced as three montelukast publications.[14] [15] [16] GINA also states "fixed combination inhalers … are usually less expensive than giving the two drugs separately." In New Zealand, Seretide® is priced 2-3 times that of the total price of separate fluticasone and salmeterol inhalers.

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[7] Best Practice Evidence-Based Guideline: The Diagnosis and Treatment of Adult Asthma. New Zealand Guidelines Group, 2002. http://www.nzgg.org.nz/library/gl_complete/asthma/index.cfm

[8] Bateman E, Britton M, Carrillo J, Almeida J, Wixon C. Salmeterol/fluticasone combination inhaler. A new, effective and well tolerated treatment for asthma. Clin Drug Invest 1998;16(3):193-201

[9] Evidence table 4.22: Combined therapy of inhaled steroids and long acting B2 agonist http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.22.html

[10] Bateman et al 1998, op cit.

[11] Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. Pediatr Pulmonol 2000;30(2):97-105.

[12] Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Can Respir J 1999;6(1):45-51.

[13] Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. Respir Med 1999;93(12):876-84.

[14] Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. J Allergy Clin Immunol 2000;105:1123-9.

[15] Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. Am J Respir Crit Care Med 1999;160:1862-8.

[16] Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. BMJ 1999;319:87-90. Cochrane Database Syst Rev 2000;2.

Recently published meta-analysis of Seretide® (Nelson et al 2003)

More recently, an industry co-written and funded meta-analysis has been published (Nelson et al 2003[17]) pooling the results of the four Seretide® RCTs behind the above BTS/SIGN statement of no difference in efficacy.

With pooling, this meta-analysis reported a significant advantage with Seretide® combination therapy over concurrent salmeterol and fluticasone therapy in morning peak expiratory flow rates (PEFR). "Odds of achieving a greater than 15 or greater than 30 L/min improvement with combination therapy were increased by approximately 40% compared with those after concurrent therapy, representing an additional 7% to 9% and 5% to 14% more patients, respectively, on combination therapy responding compared with those on concurrent therapy."

In the meta-analysis, >30 L/min improvements in PEFR with combination treatment occurred in 9% more patients (54% minus 45%), being a 19% improvement relative to concurrent controls (9%/45%).

Likewise, >15 L/min improvements occurred in an additional 7% of combination treatment patients (73% versus 66%), a relative increase of 11% (7%/66%).

These changes were reflected similarly in improvements to mean baseline morning PEFRs, where combination treatment caused on average an extra crude 5.8 L/min in PEFR over concurrent controls (38.2 vs. 32.8 L/min improvements, 5.4 L/min difference formally reported (Nelson et al 2003)).

Limitations with the Seretide® meta-analysis

However, the Seretide® meta-analysis had important limitations in its data and interpretation, materially affecting its key reported findings:

1. *Selective reporting of key findings*

   Statistically significant results in the Seretide® meta-analysis were confined to most but not all physiological variables, and there were no significant differences in more clinically-relevant outcomes (tables 1, 2 and 4, below):

   - There were statistically significant changes in self-reported mean morning and evening PEFR over weeks 1-12 (continuous variable), and achieving greater than 15 and 30 l/min improvements in morning PEFR (dichotomous variables);

   - There was no significant change in mean change in objective clinic FEV1 at week 12 (continuous variable);

   - There were no significant changes in the clinically relevant secondary outcomes of median % days and nights symptom- and reliever-free (median

[17] Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

% days symptom-free, median % nights symptom-free, median % days reliever-free, median % nights reliever-free).

Table 1

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

		PEFR combination LABA/ICS	PEFR concurrent separate LABA/ICS	% combination LABA/ICS	% concurrent separate LABA/ICS	difference	measures of effect OR(+/- 95%CI)	measures of effect RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)
physiological measures											
baseline PEFR		347.9	341.7								
>30 l/min morning PEFR increase				54.0%	45.2%	8.7%	1.42 (1.13-1.78)	1.19 (1.07-1.32)	19%	8.7%	11
clinical impact of >30 l/min increase			8.7%								
>15 l/min morning PEFR increase				72.6%	65.4%	7.2%	1.41 (1.10-1.80)	1.11 (1.03-1.18)	11%	7.2%	14
clinical impact of >15 l/min increase			4.4%								
adjusted mean change from baseline in mean morning		39.9	32.8			7.1		1.22	22%	2.1%	
WMD as published						5.4		1.16	16%	1.6%	
% change in PEFR		11.0%	9.6%			**1.4%**					
(adjusted mean change from baseline in mean morning		43.1	36.6			6.5		1.18	18%	1.9%	
WMD as published						4.7		1.13	13%	1.4%	
clinical measures											
days w/o sympts	Pharmac calculations			41.0%	39.5%	1.5%		1.04	4%	1.5%	65
median % days symptom free	WMD as published					0.0%		1.00	0%	0.0%	-
nights w/o sympts	Pharmac calculations			57.4%	53.7%	3.7%		1.07	7%	3.7%	27
median % nights symptom free	WMD as published					-1.2%		0.98	-2%	-1.2%	-87
days w/o rescue Rx	Pharmac calculations			49.7%	47.6%	2.1%		1.05	5%	2.1%	47
median % days reliever free	WMD as published					-0.4%		0.99	-1%	-0.4%	-278
nights w/o rescue Rx	Pharmac calculations			69.3%	65.4%	3.9%		1.06	6%	3.9%	26
median % nights reliever free	WMD as published					-0.1%		1.00	0%	-0.1%	-909

source: Pharmac analysis of: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

(a larger version of this table can be found at the end of this paper)

- There were significantly higher rates of adverse events reported for Seretide®, otherwise no differences in withdrawal rates/withdrawals for adverse effects.

The withdrawal and adverse events were not measured in the Seretide® meta-analysis, requiring other analysis (table 2) (further details below).

Table 2

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

	% combination LABA/ICS	% concurrent separate LABA/ICS	difference	measures of effect OR(+/- 95%CI)	measures of effect RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)
compliance								
compliance (Pharmac calculations)	93.0%	92.1%	0.9%	1.16	1.01 (0.99-1.03)	1%	0.9%	107
withdrawals and adverse events								
total withdrawals (Pharmac calculations)	14.6%	12.6%	2.0%	1.18	1.16 (0.84-1.57)	16%	2.0%	50
withdrawals from adverse events (Pharmac calculations)	8.4%	7.1%	1.2%	1.19	1.17 (0.76-1.79)	17%	1.2%	81
reported adverse events (+/- considered by investigators to be Rx-related) (Pharmac calculations)	59.0%	46.7%	12.4%	1.59	1.26 (1.09-1.44)	26%	12.4%	8

source: Pharmac analysis of: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

(a larger version of this table can be found at the end of this paper)

Note that the Seretide® meta-analysis stated a prospective sole primary outcome measure, that of morning PEFR. However, PEFR was not stated to be the primary efficacy measure for one of the RCTs (Aubier etc 1999).

Secondary measures in all the RCTs included FEV_1, and the clinically relevant outcomes.

Withdrawals and adverse events were reported for all the individual RCTs.

Withdrawals affect analysis of physiological and clinical outcomes, are themselves clinical outcomes, and should similarly have been reported. Withdrawals and adverse effects were all reported in meta-analyses of other asthma treatments, e.g. the Cochrane review of fluticasone.[18]

2. Reporting overstates the magnitude of physiological effects

In addition, Nelson et al's reporting of odds ratios (ORs) in the Seretide® meta-analysis overstates the magnitude of PEFR improvement; using relative risk (RR) gives much lower estimates of true relative effect:

- ORs (as reported by Nelson et al) are the measure used when combining results of individual trials into a weighted summary measure able to demonstrate statistically significant effects.

- Odds and ORs however do not necessarily equate to risk and relative risk (RR). If the OR is interpreted as a RR it will always overstate any effect size – particularly when baseline risk is high.[19]

- Such potential for overstatement due to high baseline risk certainly occurs with the PEFR improvements in the Seretide® meta-analysis, with 45-73% prevalence rates for both treatments and controls.

- RRs can be derived from adjusted baseline event rates and pooled odds ratios, with associated confidence limits, according to the formula[20]:

$$RR = 1 - \frac{(1-aEc).(1-OR)}{1 - [aEc.(1-OR)]}$$

  where RR = relative risk; aEc =adjusted baseline event rate (i.e. control incidence rate, weighted according to inverse variance); OR = pooled odds ratio (weighted according to inverse variance)

- Recalculating relative risks from the published ORs and calculating baseline risks gives an 11% likelihood of patients gaining =15 L/min improvement in PEFR using Seretide® rather than concurrent ICS/LABA (RR 1.11 (95% confidence interval (CI) 1.03-1.18)).

  The likelihood for a =30 L/min PEFR improvement becomes 19% (RR 1.19 (1.07-1.32)).

  These results using RRs contrast sharply with the ORs of 1.40 and 1.42 as reported by Nelson et al.

[18] Adams N, Bestall JM, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software. CD002310

[19] Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ. 1998 Mar 28;316(7136):989-91.

[20] algebraic transformation of formulae in Sackett D, Straus S, Richardson WS, Rosenberg W, Haynes B. Evidence-based medicine: how to practice and teach EBM, 2nd edition. Oxford: Churchill Livingstone, 2000. p136 Table 5.1 Formulae to convert odds ratios (ORs) and relative risks (RRs) to NNTs.

3. No difference in clinically relevant outcomes

The lack of statistically-significant clinically-relevant outcomes in the Seretide® meta-analysis reflects both (1) low variation relating to relatively small numbers of events and (2) little difference in clinically relevant outcomes:

- A 15 L/min improvement in PEFR represented just a 4.4% increase in PEFR over baseline (where patients had PEFRs averaging 344 L/min at baseline). A 30 L/min represented an 8.7% increase over baseline.

- In other words, an extra 9% of patients had a 9% or more improvement in morning PEFR through using combination treatment (and an extra 7% had a 4% or more improvement).

- Likewise, the magnitude of average improved PEFR was in the region of just 1.4% ([5.4 L/min crude mean difference in PEFR between combination and concurrent] / [344 L/min mean baseline PEFR]).

- These seemingly low physiological changes may be reflected in the very low rates of reductions in days or nights without symptoms or reliever drugs (0.0 to 1.15% reductions, all statistically insignificant).

4. No analysis of withdrawals and adverse events, where these show significantly higher rates of reported adverse events with Seretide®

The Seretide® meta-analysis could equally have analysed then reported (but did not) all withdrawals being *prima facie* 16% higher in combination than concurrent LABA/ICS users. Likewise, withdrawals due to adverse effects were *prima facie* higher at 17% with Seretide®.

Although neither measure of withdrawal showed differences that were statistically significant (see table 3), reported adverse events in Seretide® patients were significantly higher. Seretide® users had *prima facie* one quarter (26%) more reported adverse events or events considered by investigators to be drug-related (289 in Seretide® patients (59%) vs. 263 in concurrent LABA/ICS users (47%), RR 1.26, 95% CI 1.09 – 1.44) (table 3).

[To be consistent with the Nelson etc reporting of PEFR improvements in the Seretide® meta-analysis as odds ratios, the odds of reporting an adverse effect with Seretide® were increased by 59% *prima facie* compared with those after concurrent therapy (OR 1.59, 95% CI 1.16-2.17).

The use of ORs is not being advocated here. Rather the *prima facie* 1.59 OR for reported adverse events places the use of 1.40-1.42 ORs for PEFRs in context, re-emphasising how these overstate actual increases in likelihood.]

Table 3

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

	duration (weeks)	no. patients			no.		%				measures of effect				(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR	RR (+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)	
compliance															
compliance															
Bateman etc 1998	12	121	121		110	108	91%	89%	2%		1.02	2%	1.7%	61	0.3965
Chapman etc 1999	28	180	191		173	181	96%	95%	1%		1.01	1%	1.3%	74	0.2968
Aubier etc 1999															0.0000
Van den Berg etc 2000	12	125	132		116	123	93%	93%	0%		1.00	0%	-0.4%	-262	0.3067
total or weighted average	16.7	426	444		399	412	93.0%	92.1%	0.9%	1.16	1.01 (0.99-1.03)	1%	0.9%	107	1.0000
withdrawals and adverse events															
total withdrawals															
Bateman etc 1998	12	121	121		18	17	14.9%	14.0%	0.8%		1.06	6%	0.8%	121	0.2482
Chapman etc 1999	28	180	191		20	16	11.1%	8.4%	2.7%		1.33	33%	2.7%	37	0.2689
Aubier etc 1999	28	167	171		31	28	18.6%	16.4%	2.2%		1.13	13%	2.2%	46	0.4033
Van den Berg etc 2000	12	125	132		5	5	4.0%	3.8%	0.2%		1.06	6%	0.2%	471	0.0796
total or weighted average	22.8	593	615		74	66	14.6%	12.6%	2.0%	1.18	1.16 (0.84-1.57)	16%	2.0%	50	1.0000
withdrawals from adverse events															
Bateman etc 1998					11	9	9.1%	7.4%	1.7%		1.22	22%	1.7%	61	0.2585
Chapman etc 1999					12	9	6.7%	4.7%	2.0%		1.41	41%	2.0%	51	0.2785
Aubier etc 1999					16	16	9.6%	9.4%	0.2%		1.02	2%	0.2%	446	0.4076
Van den Berg etc 2000					2	2	1.6%	1.5%	0.1%		1.06	6%	0.1%	1,179	0.0554
total or weighted average					41	36	8.4%	7.1%	1.2%	1.19	1.17 (0.76-1.79)	17%	1.2%	81	1.0000
withdrawals from asthma adverse events															
Bateman etc 1998					4	3	3.3%	2.5%	0.8%		1.33	33%	0.8%	121	0.3677
Chapman etc 1999					5	5	2.8%	2.6%	0.2%		1.06	6%	0.2%	625	0.5251
Aubier etc 1999					0	0	0.0%	0.0%	0.0%		#DIV/0!	######	0.0%	-	0.0000
Van den Berg etc 2000					1	1	0.8%	0.8%	0.0%		1.06	6%	0.0%	2,357	0.1072
total or weighted average					10	9	2.7%	2.4%	0.4%	1.16 (-95% CI-+95% CI)	1.15	15%	0.4%	276	1.0000
reported adverse events (+/- considered by investigators to be Rx-related)															
Bateman etc 1998					88	69	72.7%	57.0%	15.7%		1.28	28%	15.7%	6	0.3499
Chapman etc 1999					160	164	88.9%	85.9%	3.0%		1.04	4%	3.0%	33	0.2598
Aubier etc 1999					28	24	16.8%	14.0%	2.7%		1.19	19%	2.7%	37	0.2788
Van den Berg etc 2000					13	6	10.4%	4.5%	5.9%		2.29	129%	5.9%	17	0.1115
total or weighted average					289	263	59.0%	46.7%	12.4%	1.59 (1.16-2.17)	1.26 (1.09-1.44)	26%	12.4%	8	1.0000

source: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

(a larger version of this table can be found at the end of this paper)

5. Seretide®'s physiological and clinical improvements were comparatively low

Contextually, Seretide®'s physiological and clinical improvements were low relative to those seen in other relevant ICS/LABA meta-analyses.

Patterns of Seretide® clinical improvements relative to physiological improvement were consistent with the relative patterns seen for salmeterol LABA and fluticasone (when respectively compared with increasing the dose of ICS and compared with BDP or budesonide):

- The above 5.4 L/min morning PEFR improvement with Seretide® was much less than the 22.4 L/min improvement occurring with salmeterol (when compared with increased doses of ICS – MIASMA meta-analysis[21]) or even the 13.3 L/min improvement calculable for fluticasone (when compared with BDP or budesonide) (calculating from data in figures in Cochrane review[22]).

- In the salmeterol MIASMA meta-analysis, the above 22.4 L/min magnitude of PEFR improvement was associated with a 5 to 20% relative reduction in days or nights without symptoms or reliever drugs over 3 or 6 months.

- If we assume that baseline PEFRs were similar in both MIASMA and the Seretide® meta-analyses, then the 16% relative increase in PEFR in the

[21] Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000 May 20;320(7246):1368-73.

[22] Adams N, Bestall JM, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software. CD002310

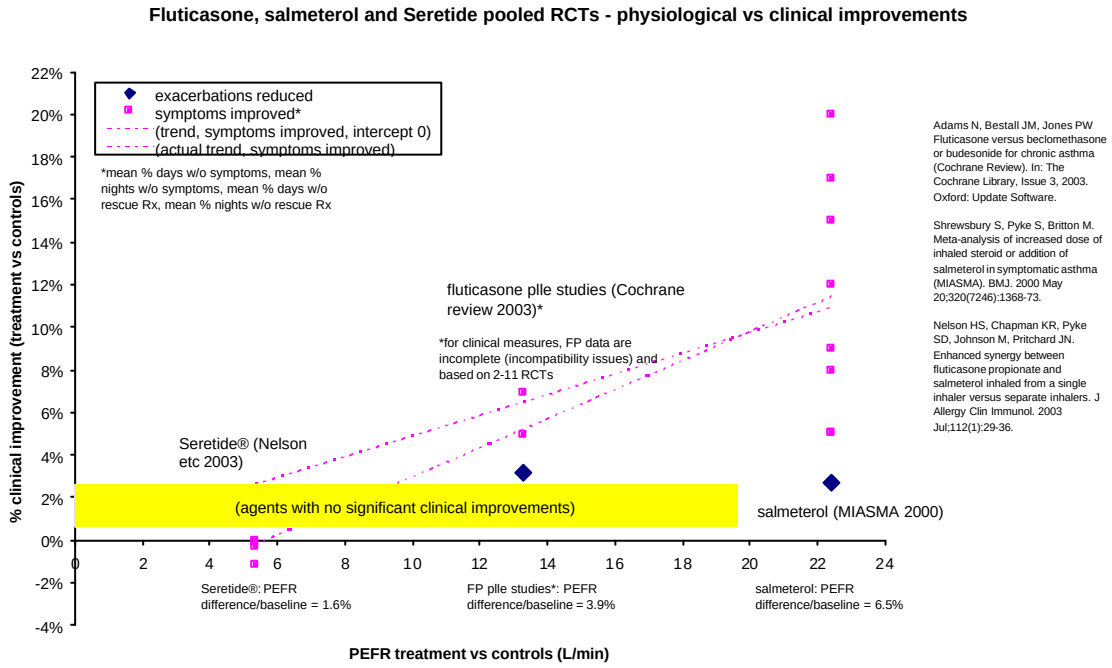
Seretide® meta-analysis[23] would translate to a 69% relative improvement with salmeterol in MIASMA[24].

- Yet such a relatively large putative relative improvement for salmeterol PEFR (RRI 69%) translates to a much smaller clinical effect (salmeterol 11% overall reduction in days or nights without symptoms or reliever drugs at 3 months, range 5 to 17%).

- This discrepancy between salmeterol's physiological and clinical effects is consistent with the contrasts seen with Seretide® between its statistically significant 5.4 L/min added PEFR improvement and its negligible clinical impacts. Incidentally, both Seretide®'s PEFR and clinical effects were appreciably lower than those of salmeterol in MIASMA.

- Likewise with fluticasone, the above 13.3 L/min improvement in PEFR translates to maybe 3% reduction in exacerbations and 6% improvement in symptom/reliever-free days (with neither overall clinical outcome statistically significant) (figure 2, table 4).

Figure 2



(a larger version of this figure can be found at the end of this paper)

[23] relative increase in PEFR with Seretide® = ([5.4 L/min difference between combined and concurrent ICSA/LABA use] / [32.8 L/min improvement with concurrent use]) = 16%

[24] relative increase in PEFR with salmeterol = ([16% Seretide® PEFR RRI] x [22.4 L/min PEFR added PEFR improvement in MIASMA] / [5.4 L/min added improvement with Seretide®]) = 69%

Table 4

Comparison between FP vs. BDP/bud RCTs (Cochrane review), Salmeterol vs. increased ICS RCTs (MIASMA), and Seretide® combination vs. concurrent FP/Salmeterol RCTs (Nelson 2003 meta-analysis)

		difference (ARR/ARI)			relative effects (RRR/RRI)		
		FP plle studies*	salmeterol	Seretide®	FP plle studies*	salmeterol	Seretide®
physiological measures							
baseline morning PEFR (L/min)		340.4	(n/avail)	344.8			
mean difference PEFR tmt vs. cntrl (L/min)	at 3 months		22.4	5.35		68%	16%
	at 6 months		27.7				
	not stated	13.3			41%		
mean difference FEV_1 tmt vs. cntrl (ml)	at 3 months		100	40			
	at 6 months		80				
	not stated	120					
extrapolated, using Seretide® 32.8 and 38.1 L/min improvements in cntrl and trmt groups (5.35 L/min difference, 16% RRI)							
clinical measures							
all exacerbations		-3.2%	-2.7%		-20%	-9%	
moderate/severe exacerbations			-2.4%				
withdrawals due to exacerbations		-1.2%		0.4%	-22%		15%
mean % days w/o symptoms	at 3 months		12%	0.00%		21%	0.00%
	at 6 months		15%				
	not stated	4.9%			15%		
mean % nights w/o symptoms	at 3 months		5%	-1.15%		19%	-2.14%
	at 6 months		5%				
mean % days w/o rescue Rx	at 3 months		17%	-0.36%		34%	-0.76%
	at 6 months		20%				
	not stated, change	6.9%			108%		
mean % nights w/o rescue Rx	at 3 months		9%	-0.11%		45%	-0.17%
	at 6 months		8%				
all exacerbations		-3.2%	-2.7%		-20%	-9%	
unweighted average symptom improvement (at 3 months, or not stated)		6%	11%	-0.41%	61%	15%	-0.38%
composite exacbns/symptoms		4.5%	6.7%	-0.2%	40.5%	12.2%	-0.2%
clinical vs. PEFR							
difference PEFR/baseline		3.9%	6.5%	1.6%			
clinical/PEFR		0.003	0.003	0.000	1.000	0.179	-0.012

*for clinical measures, FP data are incomplete (incompatibility issues) and based on 2-11 RCTs

Note that of the three ICS/LABA meta-analyses, only salmeterol has demonstrated significant clinical improvements.[25]

6. Quality of individual RCTs and meta-analysis

The above analysis has not critically appraised the four individual contributing RCTs, nor systematically appraised the meta-analysis.[26]

The four RCTs were each stated to be double-dummy double-blind randomised parallel-group controlled trials. Patients were children and adults with similar levels of asthma severity. The RCTs all measured both physiological and clinically relevant outcomes and included withdrawals and adverse events.

However, there was some ambiguity with reporting around the quality of the individual RCTs:

[25] Although clinically relevant improvements were not statistically significant with fluticasone, there were problems with study incomparability, hence possible type 1 error i.e. falsely ascribing no effect when a true effect exists.

[26] formal appraisal tools from EPIQ http://www.health.auckland.ac.nz/comhealth/epiq/epiq.htm for individual RCTs are at http://www.health.auckland.ac.nz/comhealth/ElectronicGateInterV12.doc, for meta-analyses at http://www.health.auckland.ac.nz/comhealth/epiq/GateSRChklstV3.doc

- None of the RCTs clearly described blinding;

- Three of the four RCTs did not describe the process of randomisation nor whether (and how) allocation was concealed;

- The randomisation process was described in one RCT (Bateman etc 1998), but concealment was not explicit and must be inferred from computer block randomisation;

- All patients were accounted for, but whether analysis of effectiveness was by intention-to-treat or on-treatment was unclear for one RCT (Bateman 1998), with strong inference that it was on-treatment analysis. This would mean missing out patients withdrawing because of asthma exacerbations, hence unable to contribute to data re PEFR changes;

- All were multicentre trials, but no details were given on oversight/controls across sites.

The Nelson etc 2003 Seretide® meta-analysis did not describe how its component RCTs were identified (formal search strategies etc.). That said, the separate search presumably undertaken for the BTS/SIGN guidelines' evidence table and searching PubMed revealed/reveals no other relevant RCTs. It is assumed the Nelson meta-analysis, being authored by GSK employees, would have systematically and comprehensively identified all Seretide® RCTs known to the manufacturer, but this was not made explicit in the publication.

Note again the Seretide® meta-analysis chose not to pool then report on withdrawal and adverse events rates.

Message of international guidelines remains unchanged.

Hence in view of the above limitations with the Nelson et al Seretide® meta-analysis, the advice from the BTS/SIGN, GINA and New Zealand asthma guidelines still applies, viz. that there is no difference in clinical efficacy between combination and concurrent (separate devices) LABA/ICS.

Further detail of the results of the four component Seretide® RCTs and overall pooled effects are in table 5.

Table 5

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

physiological measures

	duration (weeks)	no. patients		baseline PEFR		no.		%			measures of effect					(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT	
>30 l/min morning PEFR increase																
Bateman etc 1998	12	121	121	368	365	75	66	62.0%	54.5%	7.4%		1.14	14%	7.4%	13	0.1973
Chapman etc 1999	12	180	191	398	391	100	89	55.6%	46.6%	9.0%		1.19	19%	9.0%	11	0.3101
Aubier etc 1999	12	167	171	359	345	82	75	49.1%	43.9%	5.2%		1.12	12%	5.2%	19	0.2815
Van den Berg etc 2000	12	125	132	241	243	63	48	50.4%	36.4%	14.0%		1.39	39%	14.0%	7	0.2112
total or weighted average	12	593	615	347.9	341.7	320	278	54.0%	45.2%	8.7%	1.42 (1.13-1.78)	1.19 (1.07-1.32)	19%	8.7%	11	1.0000
clinical impact of >30 l/min increase					8.7%											
>15 l/min morning PEFR increase																
Bateman etc 1998						96	87	79.3%	71.9%	7.4%		1.10	10%	7.4%	13	0.1752
Chapman etc 1999						135	130	75.0%	68.1%	6.9%		1.10	10%	6.9%	14	0.2966
Aubier etc 1999						115	106	68.9%	62.0%	6.9%		1.11	11%	6.9%	15	0.3000
Van den Berg etc 2000						87	81	69.6%	61.4%	8.2%		1.13	13%	8.2%	12	0.2282
total or weighted average						433	404	72.6%	65.4%	7.2%	1.41 (1.10-1.80)	1.11 (1.03-1.18)	11%	7.2%	14	1.0000
clinical impact of >15 l/min increase					4.4%											
adjusted mean change from baseline in mean morning PEFR over weeks 1-12, ITTA																
Bateman etc 1998						42	33			9.0		1.27	27%	2.5%		0.2413
Chapman etc 1999						43	36			7.0		1.19	19%	1.8%		0.2892
Aubier etc 1999						35	33			2.0		1.06	6%	0.6%		0.2529
Van den Berg etc 2000						33	28			5.0		1.18	18%	2.1%		0.2167
total or weighted average				347.9	341.7	39.9	32.8			7.1		1.22	22%	2.1%		1.0000
WMD as published						38.1	32.8			5.4		1.16	16%	1.6%		
% change in PEFR						11.0%	9.6%			**1.4%**						
(adjusted mean change from baseline in mean morning PEFR over weeks 1-12, per protocol)																
Bateman etc 1998						51	42			9.0		1.21	21%	2.5%		0.1997
Chapman etc 1999						43	36			7.0		1.19	19%	1.8%		0.3125
Aubier etc 1999						40	36			4.0		1.11	11%	1.1%		0.2753
Van den Berg etc 2000						34	33			1.0		1.03	3%	0.4%		0.2125
total or weighted average						43.1	36.6			6.5		1.18	18%	1.9%		1.0000
WMD as published						41.2	36.6			4.7		1.13	13%	1.4%		

*ARI for x l/min morning PEFR increase is a measure of population impact,
= (% treatment group patients achieving xx increase) minus (% control group patients achieving xx increase).
ARI for mean changes in baseline morning PEFR is a measure of average individual clinical impact (improvement in lung function),
= (mean improvement) / (mean baseline)

clinical measures

	duration (weeks)	no. patients		no.		%			measures of effect				(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	RR	RRI	ARI*	NNT (-ve = NNH)	
days w/o sympts													
Bateman etc 1998		121	121	48	52	39.7%	43.0%	-3.3%	0.92	-8%	-3.3%	-30	0.2299
Chapman etc 1999		180	191	39	29	21.7%	15.2%	6.5%	1.43	43%	6.5%	15	0.2171
Aubier etc 1999		167	171	63	65	38.0%	38.0%	0.0%	1.00	0%	0.0%	-	0.3116
Van den Berg etc 2000		125	132	75	79	60.0%	60.0%	0.0%	1.00	0%	0.0%	-	0.2414
total or weighted average		593	615	225	225	41.0%	39.5%	1.5%	1.04	4%	1.5%	65	1.0000
WMD as published	median % days symptom free					39.5%	39.5%	0.0%	1.00	0%	0.0%	-	
nights w/o sympts													
Bateman etc 1998				58	69	47.9%	57.0%	-9.1%	0.84	-16%	-9.1%	-11	0.2224
Chapman etc 1999				84	80	46.7%	41.9%	4.8%	1.11	11%	4.8%	21	0.3364
Aubier etc 1999				95	94	57.0%	55.0%	2.0%	1.04	4%	2.0%	50	0.3065
Van den Berg etc 2000				114	99	91.0%	75.0%	16.0%	1.21	21%	16.0%	6	0.1348
total or weighted average		593	615	351	342	57.4%	53.7%	3.7%	1.07	7%	3.7%	27	1.0000
WMD as published	median % nights symptom free					52.6%	53.7%	-1.2%	0.98	-2%	-1.2%	-87	
days w/o rescue Rx													
Bateman etc 1998				75	68	62.0%	56.2%	5.8%	1.10	10%	5.8%	17	0.2159
Chapman etc 1999				73	64	40.6%	33.5%	7.0%	1.21	21%	7.0%	14	0.3182
Aubier etc 1999				63	65	38.0%	38.0%	0.0%	1.00	0%	0.0%	-	0.2935
Van den Berg etc 2000				91	104	73.0%	79.0%	-6.0%	0.92	-8%	-6.0%	-17	0.1724
total or weighted average		593	615	303	301	49.7%	47.6%	2.1%	1.05	5%	2.1%	47	1.0000
WMD as published	median % days reliever free					47.2%	47.6%	-0.4%	0.99	-1%	-0.4%	-278	
nights w/o rescue Rx													
Bateman etc 1998				82	87	67.8%	71.9%	-4.1%	0.94	-6%	-4.1%	-24	0.2446
Chapman etc 1999				126	118	70.0%	61.8%	8.2%	1.13	13%	8.2%	12	0.3999
Aubier etc 1999				117	111	70.0%	65.0%	5.0%	1.08	8%	5.0%	20	0.3555
Van den Berg etc 2000													
total or weighted average		468	483	325	316	69.3%	65.4%	3.9%	1.06	6%	3.9%	26	1.0000
WMD as published	median % nights reliever free					65.3%	65.4%	-0.1%	1.00	0%	-0.1%	-909	

source: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

(a larger version of this table can be found at the end of this paper

Table 1

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

		PEFR		%			measures of effect				
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)
physiological measures											
baseline PEFR		347.9	341.7								
>30 l/min morning PEFR increase				54.0%	45.2%	8.7%	1.42 (1.13-1.78)	1.19 (1.07-1.32)	19%	8.7%	11
clinical impact of >30 l/min increase			8.7%								
>15 l/min morning PEFR increase				72.6%	65.4%	7.2%	1.41 (1.10-1.80)	1.11 (1.03-1.18)	11%	7.2%	14
clinical impact of >15 l/min increase			4.4%								
adjusted mean change from baseline in mean morning		39.9	32.8			7.1		1.22	22%	2.1%	
WMD as published						5.4		1.16	16%	1.6%	
% change in PEFR		11.0%	9.6%			**1.4%**					
(adjusted mean change from baseline in mean morning		43.1	36.6			6.5		1.18	18%	1.9%	
WMD as published						4.7		1.13	13%	1.4%	
clinical measures											
days w/o sympts	Pharmac calculations			41.0%	39.5%	1.5%		1.04	4%	1.5%	65
median % days symptom free	WMD as published					0.0%		1.00	0%	0.0%	-
nights w/o sympts	Pharmac calculations			57.4%	53.7%	3.7%		1.07	7%	3.7%	27
median % nights symptom free	WMD as published					-1.2%		0.98	-2%	-1.2%	-87
days w/o rescue Rx	Pharmac calculations			49.7%	47.6%	2.1%		1.05	5%	2.1%	47
median % days reliever free	WMD as published					-0.4%		0.99	-1%	-0.4%	-278
nights w/o rescue Rx	Pharmac calculations			69.3%	65.4%	3.9%		1.06	6%	3.9%	26
median % nights reliever free	WMD as published					-0.1%		1.00	0%	-0.1%	-909

source: Pharmac analysis of: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

Table 2

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

	% combination LABA/ICS	concurrent separate LABA/ICS	difference	measures of effect OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)
compliance								
compliance (Pharmac calculations)	93.0%	92.1%	0.9%	1.16	1.01 (0.99-1.03)	1%	0.9%	107
withdrawals and adverse events								
total withdrawals (Pharmac calculations)	14.6%	12.6%	2.0%	1.18	1.16 (0.84-1.57)	16%	2.0%	50
withdrawals from adverse events (Pharmac calculations)	8.4%	7.1%	1.2%	1.19	1.17 (0.76-1.79)	17%	1.2%	81
reported adverse events (+/- considered by investigators to be Rx-related) (Pharmac calculations)	59.0%	46.7%	12.4%	1.59	1.26 (1.09-1.44)	26%	12.4%	8

source: Pharmac analysis of: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

Table 3

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

	duration (weeks)	no. patients		no.		%				measures of effect				(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR	RR (+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)	
compliance														
compliance														
Bateman etc 1998	12	121	121	110	108	91%	89%	2%		1.02	2%	1.7%	61	0.3965
Chapman etc 1999	28	180	191	173	181	96%	95%	1%		1.01	1%	1.3%	74	0.2968
Aubier etc 1999														0.0000
Van den Berg etc 2000	12	125	132	116	123	93%	93%	0%		1.00	0%	-0.4%	-262	0.3067
total or weighted average	16.7	426	444	399	412	93.0%	92.1%	0.9%	1.16	1.01 (0.99-1.03)	1%	0.9%	107	1.0000
withdrawals and adverse events														
total withdrawals														
Bateman etc 1998	12	121	121	18	17	14.9%	14.0%	0.8%		1.06	6%	0.8%	121	0.2482
Chapman etc 1999	28	180	191	20	16	11.1%	8.4%	2.7%		1.33	33%	2.7%	37	0.2689
Aubier etc 1999	28	167	171	31	28	18.6%	16.4%	2.2%		1.13	13%	2.2%	46	0.4033
Van den Berg etc 2000	12	125	132	5	5	4.0%	3.8%	0.2%		1.06	6%	0.2%	471	0.0796
total or weighted average	22.8	593	615	74	66	14.6%	12.6%	2.0%	1.18	1.16 (0.84-1.57)	16%	2.0%	50	1.0000
withdrawals from adverse events														
Bateman etc 1998				11	9	9.1%	7.4%	1.7%		1.22	22%	1.7%	61	0.2585
Chapman etc 1999				12	9	6.7%	4.7%	2.0%		1.41	41%	2.0%	51	0.2785
Aubier etc 1999				16	16	9.6%	9.4%	0.2%		1.02	2%	0.2%	446	0.4076
Van den Berg etc 2000				2	2	1.6%	1.5%	0.1%		1.06	6%	0.1%	1,179	0.0554
total or weighted average				41	36	8.4%	7.1%	1.2%	1.19	1.17 (0.76-1.79)	17%	1.2%	81	1.0000
withdrawals from asthma adverse events														
Bateman etc 1998				4	3	3.3%	2.5%	0.8%		1.33	33%	0.8%	121	0.3677
Chapman etc 1999				5	5	2.8%	2.6%	0.2%		1.06	6%	0.2%	625	0.5251
Aubier etc 1999				0	0	0.0%	0.0%	0.0%		#DIV/0!	######	0.0%	-	0.0000
Van den Berg etc 2000				1	1	0.8%	0.8%	0.0%		1.06	6%	0.0%	2,357	0.1072
total or weighted average				10	9	2.7%	2.4%	0.4%	1.16 (-95% CI-+95% CI)	1.15	15%	0.4%	276	1.0000
reported adverse events (+/- considered by investigators to be Rx-related)														
Bateman etc 1998				88	69	72.7%	57.0%	15.7%		1.28	28%	15.7%	6	0.3499
Chapman etc 1999				160	164	88.9%	85.9%	3.0%		1.04	4%	3.0%	33	0.2598
Aubier etc 1999				28	24	16.8%	14.0%	2.7%		1.19	19%	2.7%	37	0.2788
Van den Berg etc 2000				13	6	10.4%	4.5%	5.9%		2.29	129%	5.9%	17	0.1115
total or weighted average				289	263	59.0%	46.7%	12.4%	1.59 (1.16-2.17)	1.26 (1.09-1.44)	26%	12.4%	8	1.0000

source: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

Figure 2

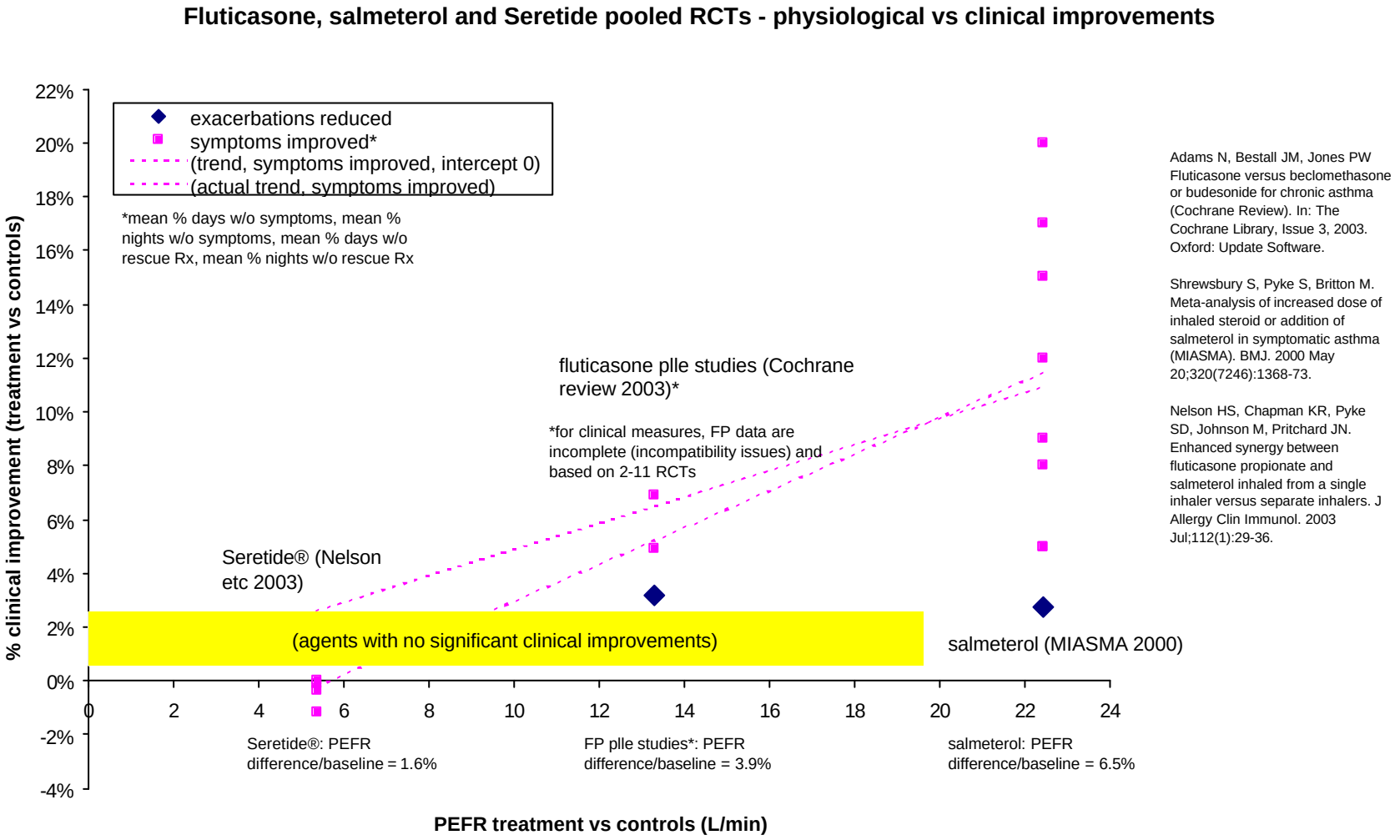


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Table 5

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

physiological measures

	duration (weeks)	no. patients		baseline PEFR		no.		%			measures of effect					(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT	
>30 l/min morning PEFR increase																
Bateman etc 1998	12	121	121	368	365	75	66	62.0%	54.5%	7.4%		1.14	14%	7.4%	13	0.1973
Chapman etc 1999	12	180	191	398	391	100	89	55.6%	46.6%	9.0%		1.19	19%	9.0%	11	0.3101
Aubier etc 1999	12	167	171	359	345	82	75	49.1%	43.9%	5.2%		1.12	12%	5.2%	19	0.2815
Van den Berg etc 2000	12	125	132	241	243	63	48	50.4%	36.4%	14.0%		1.39	39%	14.0%	7	0.2112
total or weighted average	12	593	615	347.9	341.7	320	278	54.0%	45.2%	8.7%	1.42 (1.13-1.78)	1.19 (1.07-1.32)	19%	8.7%	11	1.0000
clinical impact of >30 l/min increase					8.7%											
>15 l/min morning PEFR increase																
Bateman etc 1998						96	87	79.3%	71.9%	7.4%		1.10	10%	7.4%	13	0.1752
Chapman etc 1999						135	130	75.0%	68.1%	6.9%		1.10	10%	6.9%	14	0.2966
Aubier etc 1999						115	106	68.9%	62.0%	6.9%		1.11	11%	6.9%	15	0.3000
Van den Berg etc 2000						87	81	69.6%	61.4%	8.2%		1.13	13%	8.2%	12	0.2282
total or weighted average						433	404	72.6%	65.4%	7.2%	1.41 (1.10-1.80)	1.11 (1.03-1.18)	11%	7.2%	14	1.0000
clinical impact of >15 l/min increase					4.4%											
adjusted mean change from baseline in mean morning PEFR over weeks 1-12, ITTA																
Bateman etc 1998						42	33			9.0		1.27	27%	2.5%		0.2413
Chapman etc 1999						43	36			7.0		1.19	19%	1.8%		0.2892
Aubier etc 1999						35	33			2.0		1.06	6%	0.6%		0.2529
Van den Berg etc 2000						33	28			5.0		1.18	18%	2.1%		0.2167
total or weighted average				347.9	341.7	39.9	32.8			7.1		1.22	22%	2.1%		1.0000
WMD as published						38.1	32.8			5.4		1.16	16%	1.6%		
% change in PEFR						11.0%	9.6%			**1.4%**						
(adjusted mean change from baseline in mean morning PEFR over weeks 1-12, per protocol)																
Bateman etc 1998						51	42			9.0		1.21	21%	2.5%		0.1997
Chapman etc 1999						43	36			7.0		1.19	19%	1.8%		0.3125
Aubier etc 1999						40	36			4.0		1.11	11%	1.1%		0.2753
Van den Berg etc 2000						34	33			1.0		1.03	3%	0.4%		0.2125
total or weighted average						43.1	36.6			6.5		1.18	18%	1.9%		1.0000
WMD as published						41.2	36.6			4.7		1.13	13%	1.4%		

*ARI for x l/min morning PEFR increase is a measure of population impact,
= (% treatment group patients achieving xx increase) minus (% control group patients achieving xx increase).
ARI for mean changes in baseline morning PEFR is a measure of average individual clinical impact (improvement in lung function),
= (mean improvement) / (mean baseline)

Table 5 (cont.)

clinical measures

	duration (weeks)	no. patients		no.		%			measures of effect				(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	RR	RRI	ARI*	NNT (-ve = NNH)	
days w/o sympts													
Bateman etc 1998		121	121	48	52	39.7%	43.0%	-3.3%	0.92	-8%	-3.3%	-30	0.2299
Chapman etc 1999		180	191	39	29	21.7%	15.2%	6.5%	1.43	43%	6.5%	15	0.2171
Aubier etc 1999		167	171	63	65	38.0%	38.0%	0.0%	1.00	0%	0.0%	-	0.3116
Van den Berg etc 2000		125	132	75	79	60.0%	60.0%	0.0%	1.00	0%	0.0%	-	0.2414
total or weighted average		593	615	225	225	41.0%	39.5%	1.5%	1.04	4%	1.5%	65	1.0000
WMD as published	median % days symptom free					39.5%	39.5%	0.0%	1.00	0%	0.0%	-	
nights w/o sympts													
Bateman etc 1998				58	69	47.9%	57.0%	-9.1%	0.84	-16%	-9.1%	-11	0.2224
Chapman etc 1999				84	80	46.7%	41.9%	4.8%	1.11	11%	4.8%	21	0.3364
Aubier etc 1999				95	94	57.0%	55.0%	2.0%	1.04	4%	2.0%	50	0.3065
Van den Berg etc 2000				114	99	91.0%	75.0%	16.0%	1.21	21%	16.0%	6	0.1348
total or weighted average		593	615	351	342	57.4%	53.7%	3.7%	1.07	7%	3.7%	27	1.0000
WMD as published	median % nights symptom free					52.6%	53.7%	-1.2%	0.98	-2%	-1.2%	-87	
days w/o rescue Rx													
Bateman etc 1998				75	68	62.0%	56.2%	5.8%	1.10	10%	5.8%	17	0.2159
Chapman etc 1999				73	64	40.6%	33.5%	7.0%	1.21	21%	7.0%	14	0.3182
Aubier etc 1999				63	65	38.0%	38.0%	0.0%	1.00	0%	0.0%	-	0.2935
Van den Berg etc 2000				91	104	73.0%	79.0%	-6.0%	0.92	-8%	-6.0%	-17	0.1724
total or weighted average		593	615	303	301	49.7%	47.6%	2.1%	1.05	5%	2.1%	47	1.0000
WMD as published	median % days reliever free					47.2%	47.6%	-0.4%	0.99	-1%	-0.4%	-278	
nights w/o rescue Rx													
Bateman etc 1998				82	87	67.8%	71.9%	-4.1%	0.94	-6%	-4.1%	-24	0.2446
Chapman etc 1999				126	118	70.0%	61.8%	8.2%	1.13	13%	8.2%	12	0.3999
Aubier etc 1999				117	111	70.0%	65.0%	5.0%	1.08	8%	5.0%	20	0.3555
Van den Berg etc 2000													
total or weighted average		468	483	325	316	69.3%	65.4%	3.9%	1.06	6%	3.9%	26	1.0000
WMD as published	median % nights reliever free					65.3%	65.4%	-0.1%	1.00	0%	-0.1%	-909	

source: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.